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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/002,413	01/02/98	ALLEN R	8661-010-999

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GLADYS H. MONROY
MORRISON & FOERSTER, LLP
755 PAGE MILL ROAD
PALO ALTO CA 94304-1018

EXAMINER	
WILSON, M	
ART UNIT	**PAPER NUMBER**
1633	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/002,413	Applicant(s) Allen et al.
	Examiner Wilson, Michael C.	Group Art Unit 1633

☒ Responsive to communication(s) filed on *Sep 13, 1999*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *3-16, 18, 19, and 21-29* is/are pending in the application.

Of the above, claim(s) *24* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *3-16, 18, 19, 21-23, and 25-29* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8 and 9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Applicant's election of claims 1-23 in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The application contains claim 24 drawn to an invention nonelected with traverse in Paper No. 11 which is being treated as an election without traverse.

Claim 24 is withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 11.

Claims 3-16, 18, 19 and 21-29 are pending in the instant application. Claims 3-16, 18, 19, 21-23 and 25-29 are under consideration in the instant application.

Claim Rejections - 35 USC § 112

2. Claims 3-16, 18, 19 and 21-23 remain rejected and claims 25-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for allogenic transplantation for at least 8 months, does not reasonably provide enablement for any transplantation in any animal for any sustained period of time as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that the immune suppressive activity associated with FasL is dependent on the presence of Fas on antigen-activated T cells, not on the particular antigens involved in T cell activation; therefore, applicants argue xenogeneic transplantation is enabled. Applicants argument is not persuasive. Grisanti et al. (July 1997, Invest. Opth. & Visual Sci., Vol. 38, pages 1619-1626) of record teaches that it was unpredictable at the time of filing whether xenogeneic transplantation using RPE cells could be obtained (page 1619, column 2, 6 lines from the bottom). The immune response to an incompatible tissue is caused by the recognition of surface antigens on the tissue that are recognized by the host immune system as foreign. Without providing an adequate immune privileged site, transplanted xenogeneic tissue would be recognized as histoincompatible and destroyed by the host's immune system. The specification demonstrates isolating and culturing fetal RPE *in vitro* (pages 16-20) obtaining FasL expression by RPE and apoptosis of thymocytes contacted with the RPE (pages 21-27). The specification does not provide adequate guidance, correlate allogeneic transplantation to xenogeneic transplantation or demonstrate xenogeneic transplantation such that one of skill could obtain an immune privileged site supporting xenogeneic transplantation. Applicants have not provided adequate teachings indicating that the instant invention overcomes the ability of the immune system to recognize foreign antigens of xenogeneic, histoincompatible tissue.

Zhang et al. (May 1998, Invest. Ophthalmology & Visual Sci., Vol. 39, pages 1021-1027) of record states the immune rejection in humans is unpredictable because humans have a more heterogeneous genetic makeup than strains of laboratory animals and questions the ability to

transfer RPE cells to humans such that a therapeutic effect can be obtained (page 1021, column 2, line 13; sentence bridging pages 1021-1022; page 1026, sentence bridging columns 1 and 2). The specification does not provide any guidance how to maintain an immune privileged site in any tissue in humans such that a therapeutic effect in any disease can be obtained. Applicants have not addressed this rejection.

Ye et al. (1993, Current Eye research, Vol. 12, pages 629-639) of record teach that transplantations of allogeneic tissue were rejected by at least 8 months. Therefore, the specification does not enable obtaining immune privilege of allogeneic tissue for more than 8 months. Applicants have not addressed this rejection.

3. Claims 3-7, 9-16 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "growth factor, cytokine, ... neurotransmitter" in claims 4 and 19 remains indefinite. The phrase remains an improper Markush group because growth factors and cytokines can be inhibitors of other cytokines. Growth factors are hormones or peptide fragment of hormones. Cytokines and growth factors cause differentiation in stem cells. Growth factors can be neurotransmitters. The skilled artisan would not be able to determine whether they were infringing on the claimed invention.

Claim 3 remains indefinite because it is unclear whether "said cells" on line 4 and on line 6 refer to "RPE cells" or "cells that supply a therapeutic protein" on line 2.

Claims 25 and 29 are indefinite because the phrase "interleukin, chemokine, ...angiogenic factor" is an improper Markush group. A chemokine may be an interleukin, interferon or CSF. An angiogenic factor may be an interleukin, interferon or CSF. The skilled artisan would not be able to determine whether they were infringing on the claimed invention.

Claim Rejections - 35 USC § 102

4. Claims 3, 4, 7, 9, 12, 13, 16, 19 remain rejected and claims 25, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Ye et al. (1993, Current Eye research, Vol. 12, pages 629-639) for reasons of record set forth in the office action of 4-13-99, paper number 7.

Ye et al. teach treating retinal degeneration by administering $2.1x10^4$ allogeneic RPE cell transplants to the retina of rabbits wherein the immunologic privilege occurs and the number of RPE cells increases in the retina (see especially page 629, column 1, line 1; page 630, column 2, line 24; last line of abstract and page 631, column 2, line 20). RPE cells inherently secrete FasL and cytokines which are biologically active molecules as in claim 4. Applicant argues Ye et al. does not teach co-administration of RPE cells with cells that supply a therapeutic molecule. Applicants argument is not persuasive because the claim recites "co-administering of RPE cells with cells ... or other biologically active molecules." Therefore, Ye et al. anticipate all the limitations of the claims as written.

5. Claims 3, 4, 6, 7, 9, 10, 12, 13, 16, 18, 19, 21 and 23 remain rejected and 25, 26, 28 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record set forth in the office action of 4-13-99, paper number 7.

Cherksey teach treating Parkinson's disease using 300-3.75x10^5 RPE cells supported by a matrix transplanted in the brain of rats wherein the cells are sustained for 180 days (see the claims, especially claim 13; see also column 17, line 27; column 18, lines 25-44 and column 19, line 24) and co-administration of RPE cells with glial cells (column 9, line 2). RPE cells secrete dopamine (column 8, line 40) which is a neurotransmitter (claim 4) or chemokine (claims 4 and 19). RPE cells inherently secrete FasL and create an immunologically privileged site. Applicant argues Cherksey et al. does not teach co-administration of RPE cells with cells that supply a therapeutic molecule. Applicants argument is not persuasive because the claims recite "co-administering of RPE cells with cells ... or other biologically active molecules." Cherksey et al. teaches administering glial cells and which inherently secrete dopamine or FasL. The glial cells are a glioma cell line and allogeneic to the animal (column 8, line 59-60). Dopamine and FasL are biologically active molecules. Thus, Cherksey et al. teach co-administering allogeneic glial cells and dopamine or FasL and anticipate all the limitations of the claims.

Claim Rejections - 35 USC § 103

6. Claims 3, 14 and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) for reasons of record set forth in the office action of 4-13-99, paper number 7.

7. Claims 3, 5, 7, 8 and 11 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) in view of Goldstein et al. (U.S. Patent 5,300,436, April 5, 1994) for reasons of record set forth in the office action of 4-13-99, paper number 7.

The teachings of Cherksey et al. are cited above. It would have been obvious to re-administer cells using the teachings of Cherksey et al. because it was common practice for the ordinary artisan to repeat treatments to obtain therapeutic effects. Cherksey does not teach transfecting cells with nucleic acids encoding a protein. However, Goldstein et al. teach treating Parkinson's by transfecting cells with DNA encoding tyrosine hydroxylase (column 4, line 50), transplantation in the brain in the amount of $1\text{-}10^3$ - $1x10^7$ (column 17, line 49) and xenogeneic transplantation (column 17, line 41). Motivation to combine the references is provided by Goldstein et al. by stating the RPE cells can be transfected with tyrosine hydroxylase (column 15, lines 26-61, see line 59). One of ordinary skill would have had a reasonable expectation of success in treating Parkinson's disease by re-administering RPE cells or by using transfected cells.

Applicant argues Cherksey et al. does not teach co-administration of RPE cells with cells that supply a therapeutic molecule; therefore, applicants argue Cherksey et al. do not teach all the limitations of the claims. Applicants argument is not persuasive because the claims recite "co-administering of RPE cells with cells ... or other biologically active molecules." Cherksey et al. teaches administering glial cells and which inherently secrete dopamine or FasL. The glial cells are a glioma cell line and allogeneic to the animal (column 8, line 59-60). Dopamine and FasL are

biologically active molecules. Thus, Cherksey et al. teach co-administering allogeneic glial cells and dopamine or FasL and make obvious all the limitations of the claims.

8. The rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Cherksey (U.S. Patent 5,618,531, April 8, 1997) in view of Selawry et al. (1993, Cell Transplantation, Vol. 2, pages 123-129) and Streinlein (Nov. 17, 1995, Science, Vol. 270, pages 1158-1159) is withdrawn.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson whose telephone number is (703) 305-0120. The examiner can normally be reached on Monday through Friday from 8:30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

Michael C. Wilson

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER